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Treatment of Childhood Post-Irradiation Sarcoma of Bone in Cancer Survivors

Graziella Cefalo, MD,[1]* Andrea Ferrari, MD,[1] John D. Tesoro-Tess, MD,[3] Maria C. Gianni, MD,[1] Franca Fossati-Bellani, MD,[1] Fabrizio Lombardi, MD,[2] and Maura Massimino, MD[1]

Patients and Methods. This is a retrospective review of five children with post-irradiation bone sarcoma (PIS). Age at PIS onset ranged between 10 and 17 years (median 11). They were treated with a chemotherapy regimen, similar to that in use for primary osteogenic sarcoma, consisting of vincristine and high-dose methotrexate alternated with cisplatinum and ifosfamide, given for 12 months.

Results. In all children chemotherapy induced a complete clinical remission. Four of them were alive in continuous complete remission at 1, 2, 4, and 12 years from the diagnosis of bone sarcoma. One girl recurred 3 years from PIS diagnosis and was salvaged by repeating the same chemotherapy program: she remained alive in second complete remission 8 years from relapse.

Conclusions. In spite of an intensive treatment previously given for the primary tumor, this drug schedule proved to be feasible and short-term side effects were manageable. Chemotherapy alone, using an intensive regimen effective for primary osteogenic sarcoma, may be an adequate therapy for childhood post-irradiation sarcoma. Med. Pediatr. Oncol. 29: 568–572, 1997.

Key words: post-irradiation bone sarcoma; chemotherapy; childhood cancer survivors

INTRODUCTION

It is well known that survivors of childhood cancer represent a population at risk to develop second malignancies [1].

Since the cure rate of childhood cancers has increased over the last two decades, and an improvement in treatment modalities together with a better understanding of their natural history have been achieved, it is to be expected that the rate of patients with second tumors will increase in the future [2,3]. Of special concern is the probability of malignant second neoplasms arising within the radiation fields. Many studies have documented the association between the administration of ionizing radiation and the subsequent development of osteosarcoma [4–6].

Among second malignancies, post irradiation sarcoma (PIS) is still uncommon, but its incidence will increase according to the number of long term survivors, since its relative risk progressively rises after radiation exposure [7]. It has been calculated that the incidence of PIS ranged from 0.03–0.8% in reported series of patients with long-term follow-up [8–12]. Besides reporting on epidemiology, papers dealing with PIS provide scant information on treatment approaches, clinical management, and generally agree on the poor prognosis of this tumor with survival rates lower than 10–30% [8,13–16].

Since PIS occurs in previously irradiated areas, the most appropriate local treatment modality should consist of surgical resection, but radical surgery is rarely feasible except for PIS arising in the limbs. The use of systemic therapy for PIS is limited to a few case reports that are scarcely informative [8,13,17,18]. In order to contribute new information to the management of this overwhelming disease, we decided to report on a small series of childhood PIS of bone, occurring in a number of childhood cancer survivors, treated with a uniform chemotherapeutic approach.

PATIENTS AND METHODS

We describe a total of five children with histologically proven PIS of bone, uniformly treated in our Institution between 1984 and 1995.

[1]Division of Pediatric Oncology, Istituto Nazionale Tumori, Milano, Italy.

[2]Division of Radiation Therapy, Istituto Nazionale Tumori, Milano, Italy.

[3]Division of Radiology, Istituto Nazionale Tumori, Milano, Italy.

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*Correspondence to: Graziella Cefalo, M.D., Division of Pediatric Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milano, Italy.

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TABLE I. Patients' Characteristics

No.	Sex	Initial diagnosis	Age at RT[c] (yrs)	RT[c] (Gy) Total dose	Additional therapy	Interval to PIS[d] (yrs)	Site of PIS[d]
1	F	Ewing sarcoma	7	65	CT[a]	10	Tibia
2	F	Rhabdomyosarcoma	3	60	S[b] + CT[a]	9	Orbit
3	F	Rhabdomyosarcoma	10	54	S[b] + CT[a]	4	Pelvis
4	M	Nasopharyngeal ca.	12	65	—	3	Skull base
5	F	Rhabdomyosarcoma	6	50	CT[a]	4	Skull base

[a]CT = chemotherapy with adriamycin, vincristine, cyclophosphamide ± dactinomycin administered for 12–18 months.
[b]S = Surgery.
[c]RT = Radiotherapy.
[d]PIS = Post-irradiation sarcoma.

Table I shows the characteristics of these patients. There were one boy and four girls. Primary diagnosis included rhabdomyosarcoma-3 patients, Ewing's sarcoma, and nasopharyngeal carcinoma-1 patient each. Treatment of the primary tumor consisted of irradiation alone for the patient with nasopharyngeal carcinoma; the remaining four patients received radiotherapy plus chemotherapy with vincristine, cyclophosphamide, dactinomycin, and doxorubicin over 12–18 months. Two of five children also underwent resection of their primary tumor. Patients' age at the time of radiation therapy ranged from 3–12 years, with a median age of 7 years. Doses to the areas in which bone sarcoma developed ranged from 50–65 Gy, with a mean dose of 60 Gy. All children received megavoltage radiation therapy. The latency period ranged from 3–10 years, with a median of 4 years.

All of the patients were on active follow-up and under periodical clinical and radiological surveillance when PIS was detected. In 3 of five children the diagnosis was based only on radiological findings, while 2 also complained of clinical symptoms. In each case the diagnosis of PIS was confirmed through an open biopsy. In no case metastases from PIS were revealed.

Histological diagnosis of PIS was performed according to the criteria proposed by Cahan and co-workers in 1948 [5], and modified by Arlen et al. in 1971 [19]. Criteria were the following: (a) primary malignant tumor devoided of osteoblastic activity, histologically demonstrated; (b) development within the radiation field; (c) relatively long latency period, at least 3 years; and (d) histologic proof of sarcoma.

Treatment of PIS was chemotherapy in all patients. Surgery was feasible in one case only and was performed after two months after starting chemotherapy (Table II).

Chemotherapy consisted of the regimen in use in our Institution for primary osteogenic sarcoma, with vincristine (1.4 mg/sqm) plus high-dose methotrexate (8 g/sqm) administered on day 1 and 8 with leucovorin rescue (15 mg every 6 hours × 12 starting 24 hours after initiating methotrexate infusion), followed by cisplatinum (40 mg/sqm) plus ifosfamide (1.5 g/sqm) on days 15–17. This schedule had to be repeated monthly for a total treatment duration of 12 months.

When methotrexate clearance and/or kidney function tests (serum BUN, creatinine, and β_2 microglobulin, urinalysis, creatinine-clearance) were found abnormal in two subsequent cycles, the high-dose methotrexate (HD-MTX) administration on day 8 was deleted and monthly cycles of vincristine plus HD-MTX alternated with cisplatin plus ifosfamide were adopted. This also favored the recovery from myelotoxicity between cycles, avoiding an excessive delay of treatment.

Tumor response to chemotherapy was evaluated clinically every month and by radiological and scintigraphic examinations every three months.

RESULTS

Table II also describes the outcome of the five patients.

A median of 6 cycles of chemotherapy (range 5–8) were administered for a duration of 10–14 months.

The chemotherapy regimen obtained a complete clinical and radiological remission in all patients. Histological examination performed in the only patient submitted to surgery after the second cycle of treatment showed 100% necrosis (grade IV according to Rosen's classification) [20].

At the time of this analysis four patients were alive in continuous complete remission at 1, 2, 4, and 12 years from the time of PIS diagnosis. The only patient who recurred locally 4 years after PIS diagnosis, was salvaged by repeating the same treatment program for 8 additional cycles (Figures 1 and 2 show radiological findings at PIS onset and after treatment). This patient was alive in second complete remission 8 years from relapse, and was delivered of a healthy child 3 years after the conclusion of chemotherapy.

In this series of patients previously treated with chemotherapy plus irradiation of primary tumor, the degree and frequency of hematological, hepatic and gastro-

TABLE II. Treatment, Response, and Outcome of Post-irradiation Sarcoma (PIS) of Bone

No.	No. of CT cycles	Response	Surgery	Survival from PIS diagnosis (yrs)	Status
1	5[b]	CR	Amputation[a]	12	NED
2	6[b]	CR	None	11	2nd CR[d]
3	6 (5[b] + 1[c])	CR	None	4	CCR
4	8 (3[b] + 5[c])	CR	None	2	CCR
5	6 (2[b] + 4[c])	CR	None	1	CCR

[a]Surgery performed after 2 cycles of chemotherapy.
[b]Monthly cycles of vincristine + methotrexate/vincristine + methotrexate/cisplatin + ifosfamide.
[c]Monthly cycles of vincristine + methotrexate/cisplatin + ifosfamide.
[d]In 2nd CR 8 years from relapse, after 8 further cycles of the same chemotherapy schedule.

intestinal acute toxicity were similar to those observed in patients treated for primary osteogenic sarcoma.

In all patients abnormal renal function represented the most common acute side effect, requiring as the only measure drug schedule modifications, as previously described. So far, follow-up kidney function tests, including tubular and glomerular function evaluation, as well as renal scan demonstrated normal findings in each patient. At the time of present analysis, no long-term sequelae were observed. As to ototoxicity, we have to underline that no audiometric tests were performed in these patients, provided that none showed any clinical sign.

DISCUSSION

Post-irradiation bone sarcoma represents one of the most frequent second malignant neoplasms in childhood cancer survivors. In the literature several papers deal with epidemiological, pathological and radiological findings [8,21–26], with scanty information available on therapeutic strategies.

Currently, therapeutic results are poor: PIS is reported to have a worse prognosis than primary osteogenic sarcoma. The majority of tumors shows a high histological grade and aggressive behavior, but the poor outcome is

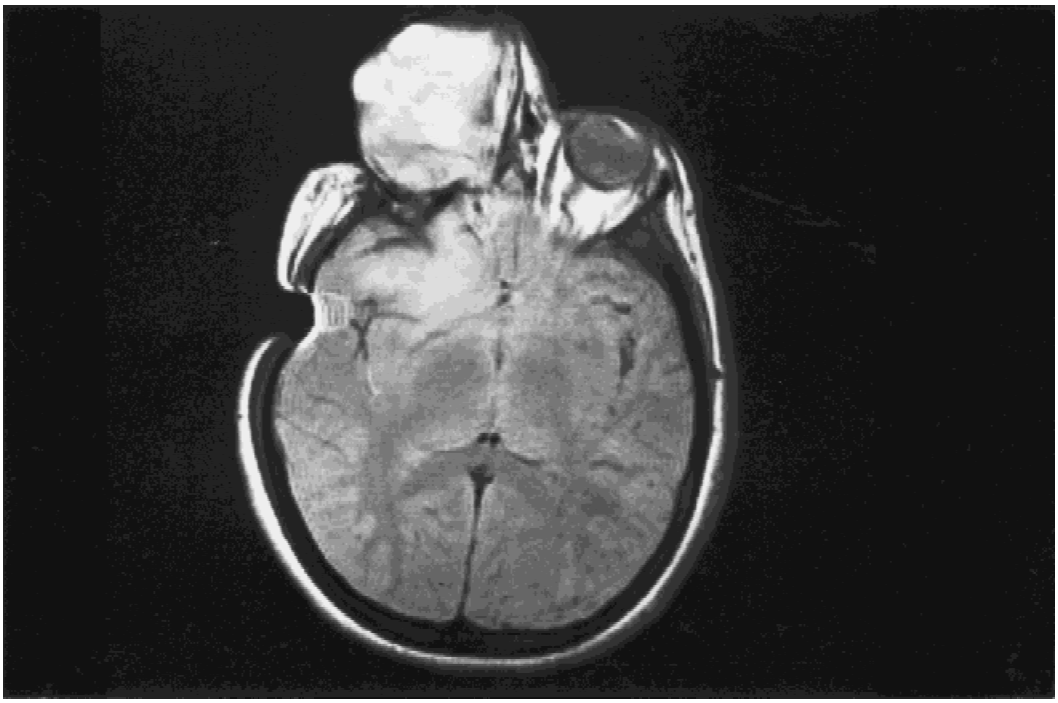

Fig. 1. Post radiation osteosarcoma of the right orbit (patient ≠2 in Table I) MRI showing the extension of the PIS at diagnosis.

Fig. 2. MRI showing the complete remission of PIS (patient #2) at the end of treatment (chemotherapy alone without any additional surgery).

also related to the tumor site. In previously irradiated areas clinical diagnosis is more difficult and often delayed, because symptoms and radiological imaging are frequently difficult to evaluate. Furthermore, PIS is often located in areas where radical surgery, which is the best chance for cure, cannot be performed, and radiation therapy is not recommended because tissues have already been exposed to irradiation.

The use of chemotherapy is limited to a few case reports [18] with various schedules including different drug sequences, and no proof is available on the effectiveness of chemotherapy. Kuten [17] reported on the failure of the CYVADIC combination regimen in post-irradiation soft tissue sarcoma occurring in breast cancer patients. Fibrotic changes following previous irradiation lead to inadequate blood supply that is supposed to produce insufficient drug concentration in the target organ. Huvos [13] reported no benefit from primary chemotherapy with high-dose methotrexate followed by surgery and adjuvant chemotherapy in post-irradiation osteogenic sarcoma of bone.

Conversely, the results obtained with our regimen including vincristine, high-dose methotrexate, cisplatin, and ifosfamide were interesting, despite the small number of patients. We obtained five complete remissions using chemotherapy alone, and the patient who underwent surgery after two chemotherapy cycles showed 100% tumor necrosis on histological examination. Only one girl recurred and was salvaged by repeating the same chemotherapy regimen. All the patients were alive without evidence of disease at a median follow-up of 4 years (range 1–12).

Response to treatment was higher than reported in the literature, where the 2 and 5-year survival rates varied from 22%–45%, and from 11%–30%, respectively [13–16,22,26]. A better survival rate (67% at 5 years) was reported only for patients treated with either radical surgery or combined marginal surgery and post-operative re-irradiation when feasible [26].

We speculated that the prolonged exposure to, and the cumulative dose of antiblastic chemotherapy could overcome the intrinsic chemo-resistance of the irradiated tissues, thus obtaining a fair percentage of objective responses.

Early diagnosis can also contribute to the success of treatment. In former times, PIS was diagnosed at advanced stages, because long-term follow-up of cancer survivors was not as regularly scheduled as nowadays [26].

This is a small series of patients with post-irradiation bone sarcoma homogeneously treated in which an excellent response to chemotherapy was demonstrated. In spite of an intensive treatment previously given for primary tumor, the drug schedule we adopted proved to be feasible and acute side effects were manageable and transient.

We might conclude that chemotherapy alone, using an intensive regimen effective in primary osteogenic sar-

coma, may be adequate therapy for PIS. However, a longer follow-up is needed to confirm the favorable outcome of these patients.

The present report also confirms that a continuous surveillance is necessary for long-term survivors of childhood cancer.

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